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BEHAVIORAL EFFECTS OF BENACTYZINE ON EQUILIBRIUM MAINTENANCE AN--ETC(U)
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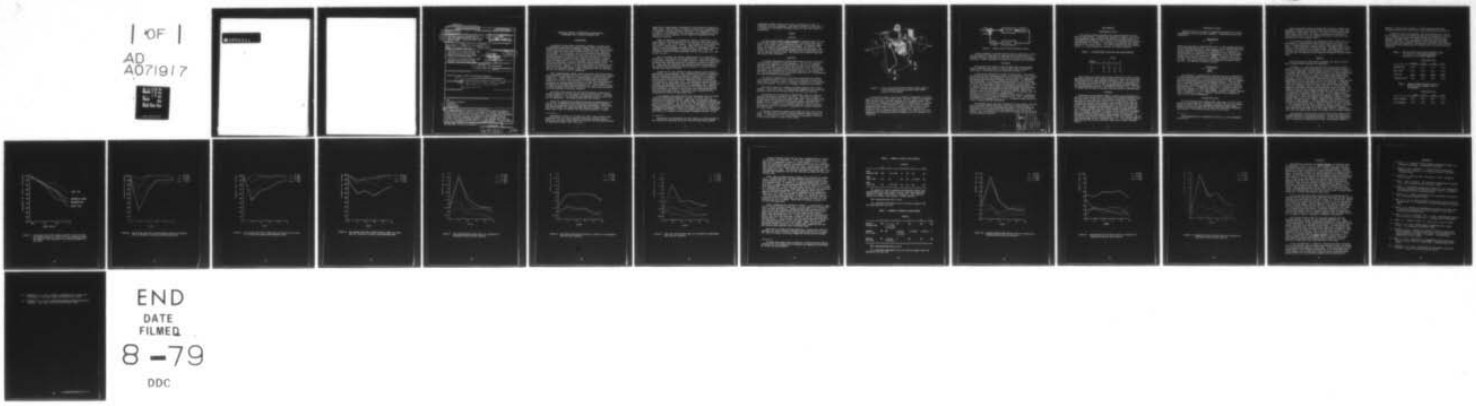

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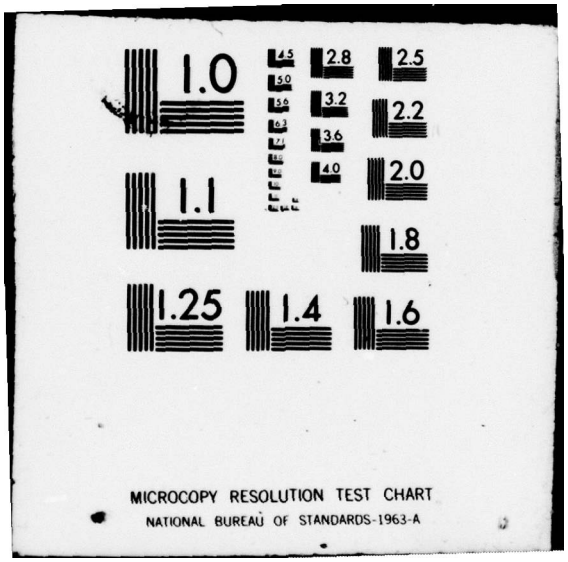
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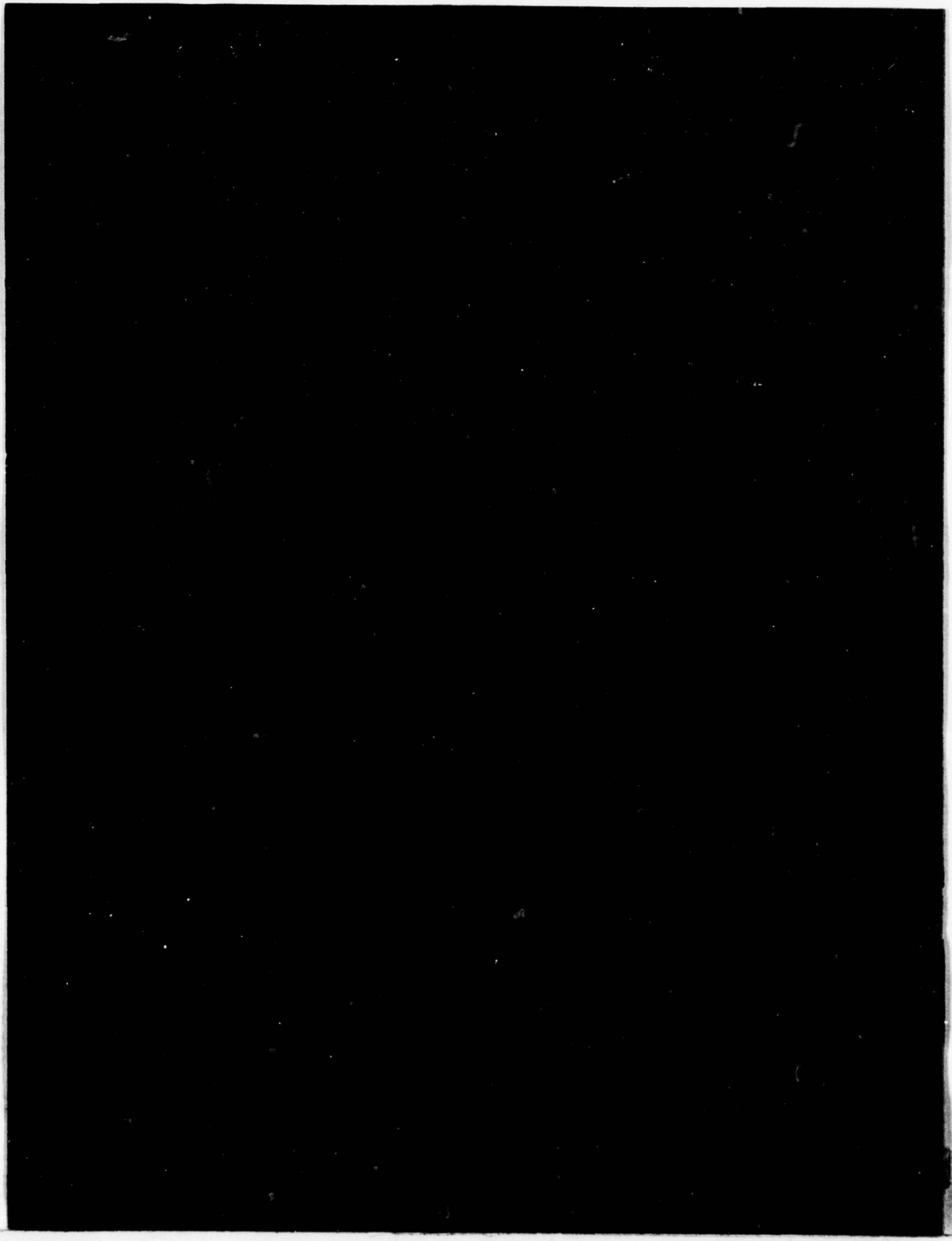

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Four Macaca mulatta were tested for performance changes following exposure to benactyzine at 4 doses ranging from 0.054 mg/kg to 1.7 mg/kg. Performance tests included adjusted root mean square error scores obtained from the USAFSAM Primate Equilibrium Platform, and response time scores obtained from the Multiple Alternative Response Task apparatus. Dose response curves were obtained using these performance measures. It was concluded that 0.054 mg/kg was near a performance sign-free dose in the Macaca mulatta. Disruptive performance can be expected at 1.7 mg/kg of benactyzine in this species.

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BEHAVIORAL EFFECTS OF BENACTYZINE ON EQUILIBRIUM MAINTENANCE AND A MULTIPLE RESPONSE TASK

INTRODUCTION

A mixture of three drugs, benactyzine, atropine, and TMB_4 (N,N'-trimethylenebis-[pyridine-4-aldoxime bromide]) known as TAB, has been proposed for field use for preliminary treatment of nerve gas poisoning. Pilot studies have shown that a single dose of TAB which consists of 39.2 mg TMB_4, 1.0 mg atropine, and 4.1 mg benactyzine was moderately detrimental to the performance of normal men, and that two doses were severely damaging to one's ability to function effectively.[1] These side effects were observed to start within minutes of the injection, reach a maximum effect at 30 to 45 minutes, then gradually recede. The protective properties of TAB are such that maximum benefit can be derived from this antidote if it can be given prior to exposure to the nerve gas poison. However, if a nerve agent attack was not confirmed and the unit commander ordered troops to administer TAB, the ability of the unit to function could be jeopardized.

Both organophosphate poisons (nerve gas agents) and TAB are powerful psychoactive compounds that have a variety of central nervous system effects (8). Indeed, exposure to organophosphate pesticides has been suggested as a major cause of aircraft accidents among crop duster pilots (6, 9, 11, 13). The anticholinergic drugs that are administered as therapy for organophosphate poisoning have also been suggested to interfere with efficient flying performance (9). Both of these classes of compounds affect mechanisms of attention and visual-motor integration which are essential in aircraft operation.

Benactyzine and atropine are the anticholinergics in TAB and are probably responsible for the central nervous system effects. Synergism is also possible, so the individual and combined effects of these drugs must be understood. A few human studies have been helpful.

Larsen (5) examined human subjects following the administration of 2 mg or 5 mg of benactyzine and found minimal performance decrements. Although the performance level was generally satisfactory, Larsen noted that these subjects did experience some subjective changes. At the higher dose (5 mg), he reported the drug caused blocking of thought,

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[1]Performance studies of the effects of TAB on human subjects were conducted at the U.S. Army Biomedical Laboratory, Aberdeen Proving Ground, Md, and results were reported in the Food and Drug Administration IND Application Number 12129, 1977, Sup 1.

impairment of recent memory, impairment of time perception, feeling of "heavy limbs" (although muscle contraction measured by a dynamometer was not affected), ataxia, dizziness, drowsiness, and inappropriate bursts of laughter. The findings at the lower dose (2 mg) indicated very mild symptoms in 48 of 56 subjects, and no subjective complaints for the remaining 8 subjects.

Coady and Jewesbury (2) studied the effects of benactyzine on 72 human subjects, and concluded that 2 mg could cause some subtle performance changes in 40% of the subjects. The duration of these effects was very short (a few minutes). At 7 mg, Coady noted that his subjects seemed to experience thought blockage, breaks in conversation, and were impaired in the performance of the serial sevens test. This test requires the subject to count backwards from 100, by sevens, e.g., 100, 93, 86, 79, etc.

Hess and Jacobsen (4) tested 1 human subject at a 12-mg dose of benactyzine. This subject was incapacitated for a short time; however, he was greatly improved in 1 hour and 40 minutes. Hess and Jacobsen also reported slower reaction times and an increase in errors at a dose of 6 mg. These data also indicated that subjects tended to concentrate on one stimulus while ignoring the second stimulus in a study of choice reaction time (buzzer vs. bell).

Vojvodic et al. (12) studied 30 human volunteers using atropine, benactyzine, and pralidoxime. They concluded that wearing a protective mask and appropriate protective clothing in addition to the injected mixture of the drugs caused markedly poor performance on a standard military obstacle course as well as exhibiting a loss of accuracy in their ability to aim an Army rifle. The experimental design included a placebo control group which allowed the conclusion that the mixture of the drugs was responsible for much of the performance loss. However, these Yugoslavian investigators tested for the effects of benactyzine and pralidoxime, and there is some evidence that pralidoxime does not cross the blood brain barrier. Therefore, their findings could be interpreted as effects of benactyzine alone.

It is apparent from these reports that benactyzine alone can cause significant performance decrement. However, the proper ratio of atropine and benactyzine with the oxime, TMB_4, can, perhaps, maintain the protective properties of this antidote while reducing the detrimental behavioral side effects. The current ratio of benactyzine, atropine, and TMB_4 was arbitrarily selected, and this series of studies is a part of a comprehensive program to improve the efficacy of TAB while reducing the detrimental side effects.[2] Thus, the overall purpose of this investigative effort is to examine the performance decrement potential of each

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[2]Benactyzine was selected as the first drug to be tested because it has psychoactive properties which are less well known than atropine.

constituent of TAB, so that a new ratio of constituents of TAB, if indicated, could be formulated. The specific purpose of this paper is to identify the performance decrement curves for four dose levels of benactyzine.

METHOD

Subjects

Six male rhesus monkeys (Macaca mulatta), weighing between 5.5 and 7.0 kg, were randomly selected and trained. The subjects were naive prior to this study, having no previous training or laboratory experience. Two subjects were intended as replicates. One subject, #572, became ill during the experiment and was omitted from the study. The utility of a second replicate was therefore greatly diminished and he was also omitted from the study. The results are therefore based upon data gained from 4 subjects.

Apparatus

The Primate Equilibrium Platform (PEP) shown in Figure 1 was used as the primary apparatus in this experiment. The PEP is a simulator gimbaled to be capable of rotations about two axes (pitch and roll). For this experiment, only the pitch axis was used and the platform was held stable in a horizontal position about the roll axis. The platform was driven from horizontal by an externally generated input signal, in this case quasi-gaussian white noise with a band width of .3 Hz generated by a Hewlett-Packard noise generator.

The subjects compensate for this input by manipulating a control stick mounted directly in front of them. By effectively tracking the input signal the subjects learn to maintain the platform in a relatively horizontal position. Figure 2 is a schematic diagram of this system.

The subject reacts to a change in platform position with a stick movement. This stick signal is algebraically summed with the externally generated input and the resultant signal now drives the platform.

The position of the platform is determinable using the output of follow potentiometers attached to the chair. This signal is used to determine the adjusted root mean square (RMS) error of the platform (the primary measure of performance used in this study). Adjusted RMS is a measure of the variability of the platform position about the mean. As such, it is a measure of the subject's ability to control the platform position using the joystick to compensate for changes induced by the input signal.

A Multiple Alternative Response Task (MART) was also used in this study. The MART panel contains 5 stimulus-response lights as shown in Figure 1. The position of the MART relative to the primate (left side of the control stick) is shown in this figure.

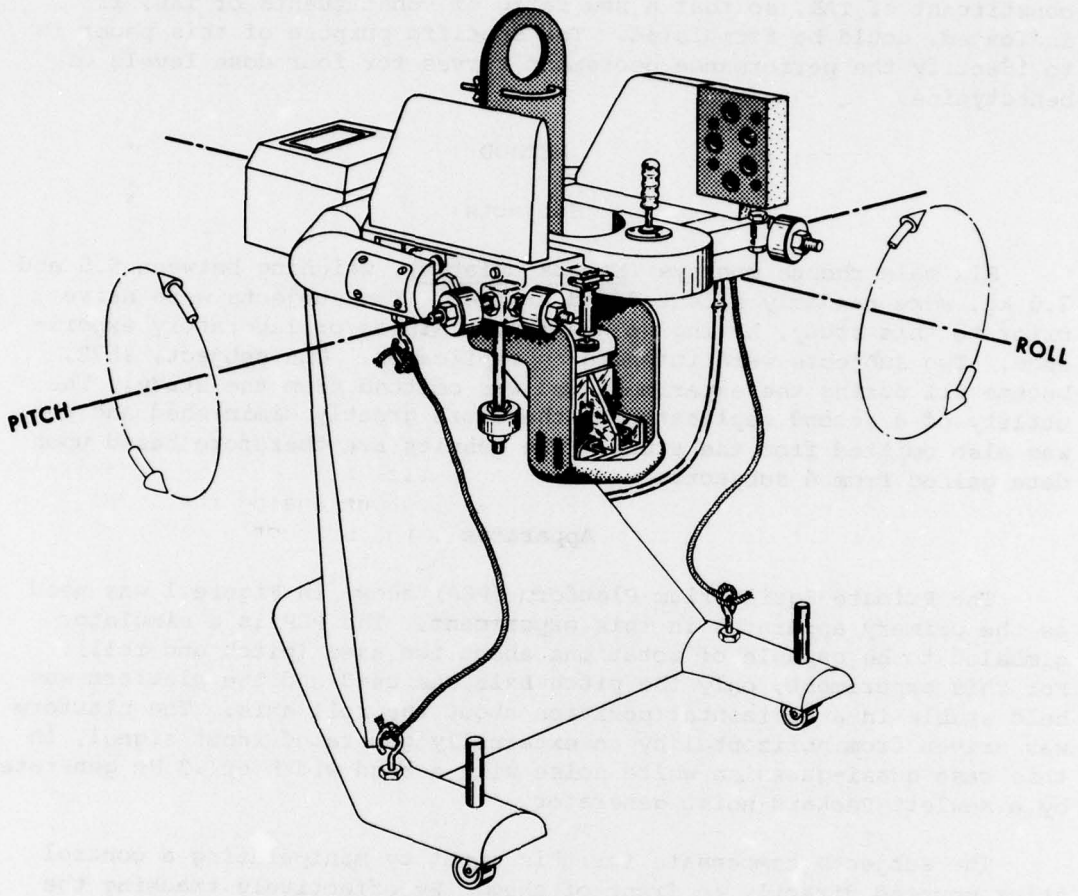

Figure 1. Primate Equilibrium Platform (PEP) showing position of the Multiple Alternative Response Task (MART) relative to the primate.

The stimulus-response units are arbitrarily designated as an alert light (yellow) and 4 fire lights (red). The fire lights are equidistant from the alert light to assure comparability of response times. The alert light is illuminated (concurrent with a 1000-Hz tone) to initiate a trial sequence. The primate must touch the light within 5 seconds. Immediately upon making a correct response, the alert light is extinguished and one of the fire lights is illuminated, requiring the primate to make an immediate second response. The order of fire light presentation is balanced although the sequence of such presentation is randomized.

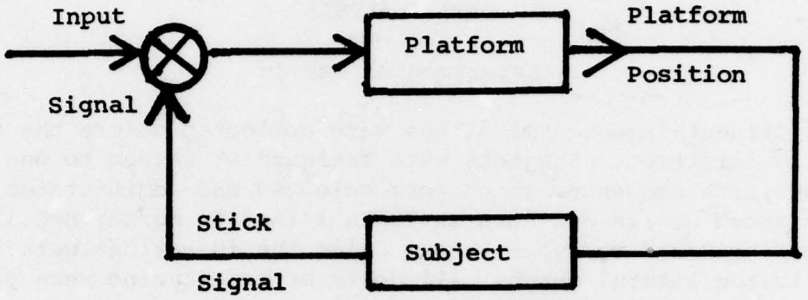

Figure 2. Control loop of the PEP-subject system.

Primate responses to the PEP control stick are relatively continuous and defined by comparison of input and output analog functions, whereas responses to the MART are discrete; the subject's performance, therefore, is best described by accuracy and response time parameters.

Procedure

The subjects were trained to PEP and MART tasks using standard operant techniques with electric shock as motivation to respond to these tasks. This method has been described by Barnes (1).

A test period consisted of 3 hours of work per day. This period was divided into six 30-minute sessions, each consisting of ten 3-minute epochs in which data were sampled for 102.4 seconds at 10 samples/sec. The sampled data were used to compute for each epoch: the adjusted RMS of platform, σ; the average platform position, μ; and the average response time and percent accuracy for the alert and fire lights. RMS, ψ, is the root mean square value of instantaneous platform position. It measures how well the platform is being maintained "level and still" about 0°. Adjusted RMS measures how well the subject controls the platform about its mean position in the event that the subject does not maintain a horizontal platform. Mathematically, $\sigma^2 = \psi^2 - \mu^2$. A discussion of the behavioral sensitivity of these metrics in assessing PEP performance can be found in Yochmowitz et al. (14). Perfect PEP performance is synonymous with $\psi = \sigma = 0$. In general, small values for ψ and σ indicate good PEP performance.

The PEP/MART system operated continuously for one session, was idle while the animal subject was given an injection (control diluent, or benactyzine at one of the prescribed dose levels), and the system was restarted to run continuously for the remaining 2 1/2 hours of the period. Thus, one session was a preinjection session, and five sessions were postinjection sessions.

DATA ANALYSIS

Experimental Design

Four diluent-injected baselines were collected before the first dose was administered. Subjects were assigned at random to one of the four benactyzine sequences which were selected and administered in a counterbalanced design as shown in Table 1 (A=0.54 mg/kg; B=0.17 mg/kg; C=0.054 mg/kg; D=1.7 mg/kg). In all cases the injections were intramuscular in the lateral thigh. All doses of benactyzine were prepared by the U.S. Army Biomedical Laboratory (Lot Number 770930-B).

TABLE 1. COUNTERBALANCED DESIGN FOR DRUG ADMINISTRATION

	Trial			
Subject	1	2	3	4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C

Each subject was tested under diluent conditions at least one day immediately preceding each treatment condition to make sure the subject had returned to his normal baseline performance range. The lowest dose (0.054 mg/kg) was selected because it is the amount of benactyzine in one TAB autoinjector which is the recommended human antidote treatment for organophosphate poisoning. The higher three doses (0.17, 0.54, and 1.7 mg/kg) were selected as one-half log units above the standard dose.

Incidence

Examination of performance effects incidence was accomplished by fitting a least-squares line to 4 diluent runs preceding treatment doses and constructing a region of normal behavior around this line using simultaneous tolerance limits (P=0.95; α=0.05) described by Rahe (7). Treatment performance values outside these confidence bands indicate a statistically significant performance effect at the α=0.05 level for P=0.95. This technique has been applied in reaction time experiments by Yochmowitz and Brown (15) and in PEP studies by Yochmowitz et al. (16). Multiplying the number of 3-minute epochs outside the confidence band by 3 minutes, results in an estimate of the time each subject's performance differed significantly from preexposure performance. To indicate how the subjects perform overall on both the continuous PEP and the discrete MART, we use a composite score, i.e., the average number of times adjusted RMS and fire and alert times were in normal tolerance limits.

Magnitude of Change

Modified Z-scores were used to determine the magnitude of change in performance metrics following treatment. Traditional Z-scores are defined by:

$$Z = \frac{x_{Treatment} - \mu_D}{\sigma_D}$$

where μ_D is the mean or expected value and σ_D is the standard deviation of the preceding diluent runs (and $x_{Treatment}$ is the adjusted RMS, alert or fire time observed under a given treatment dose). To account for subject fatigue or improvements in performance, μ_D was replaced by y_p, the predicted score based upon the least-squares fit to the preceding diluent run, and σ_D was replaced by $-\sqrt{RMS}_p$, the square root of the residual mean squared error of the regression analysis in determining the line. Thus σ_D was replaced by the unexplained variability about the line. The modified Z-statistic becomes:

$$Z = \frac{x_{Treatment} - y_p}{\sqrt{RMS}_p}$$

By converting to standard units (Z-scores) one has a common metric to compare behavior between reaction times and adjusted RMS scores as well as between subjects. In each case one knows the number of standard deviations separating predicted and observed behavior. Z-scores less than -3 represent unusually good performance relative to the previous diluent run. Conversely, Z-scores in excess of +3 represent unusually poor performance.[3] In computing standard units, one has the option of doing best, average, or worst case analyses. In examining reaction times, for instance, one can select minimum, average, or maximum reaction time to represent $x_{Treatment}$. Finally, Z-scores can be examined in terms of their time to occurrence.

Significance Tests

For each variable (mean adjusted RMS, alert time, and fire time Z-scores) and every session, an analysis of variance for the Latin square design was used to test for performance differences between doses. Duncan's (3) multiple range test was used when significant differences were detected. All testing was done at the α=0.05 level.

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[3]These guidelines are conservative in that Z = $\pm$ 1.96 corresponds to an α= 0.05.

ANOVA and multiple range techniques were not used to compare time intervals (sessions) since (mean) Z-scores are sufficient to make these comparisons. Three cases can occur: (1) session A and session B both have Z-scores less than 3; (2) session A and session B both have Z-scores greater than 3; and (3) session A's Z-score is less than 3 and session B's Z-score is greater than 3.

In the first case subjects are performing within normal limits in both sessions. By definition, their session behavior is normal. To say it is significantly more normal than the other session makes no sense. In the second case, subjects exhibit a treatment effect in both sessions. Their behavior is no longer normal. The magnitude of their Z-scores will indicate which session had the poorest performance. In the last case, the session with the smallest Z-score had the best performance.

RESULTS

All data reported in this section represent the results obtained from 4 subjects which completed the experiment.

Incidence, i.e., the average percent time within normal diluent ranges, is shown in Table 2 and Figure 3 for postinjection sessions 2-6 vs 4 diluent baselines. Average response accuracy is given in Table 3. The average time within normal (diluent) limits is inversely proportional to dose as seen in Figure 3. At the 0.054 mg/kg dose, adjusted RMS, alert time, and fire time performance was within normal ranges 99% of the time. At the 0.17 mg/kg dose these three metrics were normal approximately 91.5% of the time. At the 0.54 mg/kg dose, normal behavior ranged from 74.5% for adjusted RMS to 92% for fire time. A composite score, the average of fire time, alert time, and adjusted RMS percent time within tolerance limits, is shown in Figure 3. It is an overall measure of performance for both the discrete and continuous tasks. The composite score is also inversely proportional to dose as expected. At 1.7 mg/kg incidence scores ranged from 66% for alert time to 81.5% for fire time with a composite score of 73.8%. At the 2 highest doses, adjusted RMS and alert time exhibited the greatest incidence of changes in performance. These data suggest that performance changes can occur between 0.054 mg/kg and 0.17 mg/kg. Figures 4-6 show incidence as a function of time (session). The most dramatic performance disruptions occurred in adjusted RMS (Fig. 4) and fire time (Fig. 5) during session 2. An ordering effect by dose is evident in these 2 figures. In these cases the greater the dose, the greater the performance disruption. This ordering was not clear-cut in alert times (Fig. 6). However, in this case, the highest dose tested (1.7 mg/kg) had the greatest effects.

The magnitude of effects based upon Z-scores closely parallels the incidence findings in the ordering of doses. Figures 7-9 present the Z-score data for the average-case analysis. Note the mean adjusted RMS (Fig. 7) ordering of doses from low to high, the greatest effects at

session 2, and Z-scores in excess or 3 units during the half-hour following injection with their return 1-hour postinjection (session 3).

Effects for alert light response time means Z-scores (Fig. 8) were not as marked in that the ordering was not as distinguishable. However, the 1.7 mg/kg dose Z-scores were high although none of the Z-scores exceeded 3 standard units. An ordering of doses for mean fire light response times (Fig. 9) emerged again with the performance following the 1.7 mg/kg dose exceeding 3 standard units during the first half-hour postinjection and returning below 3 standard units 1-hour postinjection (session 3).

TABLE 2. AVERAGE PERCENT TIME WITHIN TOLERANCE LIMITS ($P = 0.95; \alpha = 0.05$) FOR POSTINJECTION SESSIONS 2-6 VS. 4 DILUENT BASELINES

	Benactyzine dose			
	0.054	0.17	0.54	1.7
Adjusted RMS	98.5	92.5	74.5	71.0
Alert time	100.0	90.0	84.0	66.0
Fire time	99.0	92.0	92.0	81.5
Composite score	99.2	91.5	83.5	73.8

TABLE 3. AVERAGE PERCENT ACCURACY SCORE FOR ALERT AND FIRE RESPONSES FOR ALL SIX SESSIONS

	Benactyzine dose			
	0.054	0.17	0.54	1.7
Alert response	98.2	99.5	98.5	93.0
Fire response	99.7	99.8	99.3	96.3

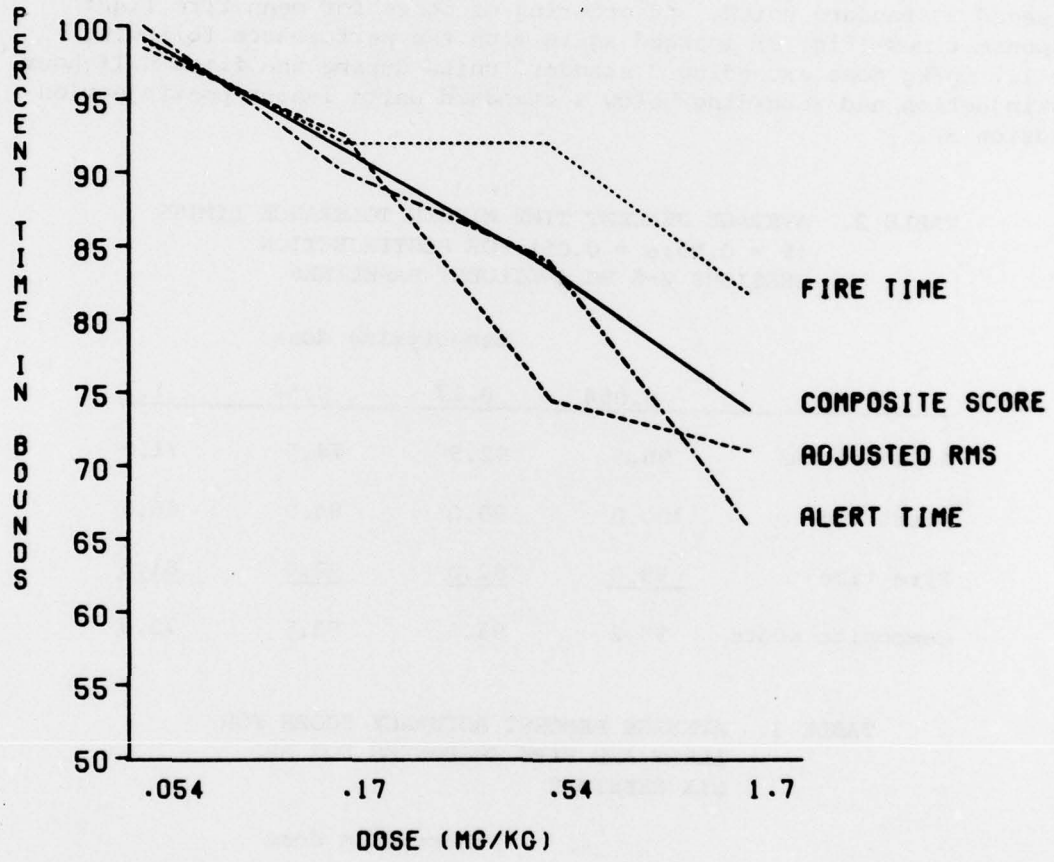

Figure 3. The average time within normal (baseline) limits for each performance measure as a function of the benactyzine doses. The composite score represents the average performance at each dose.

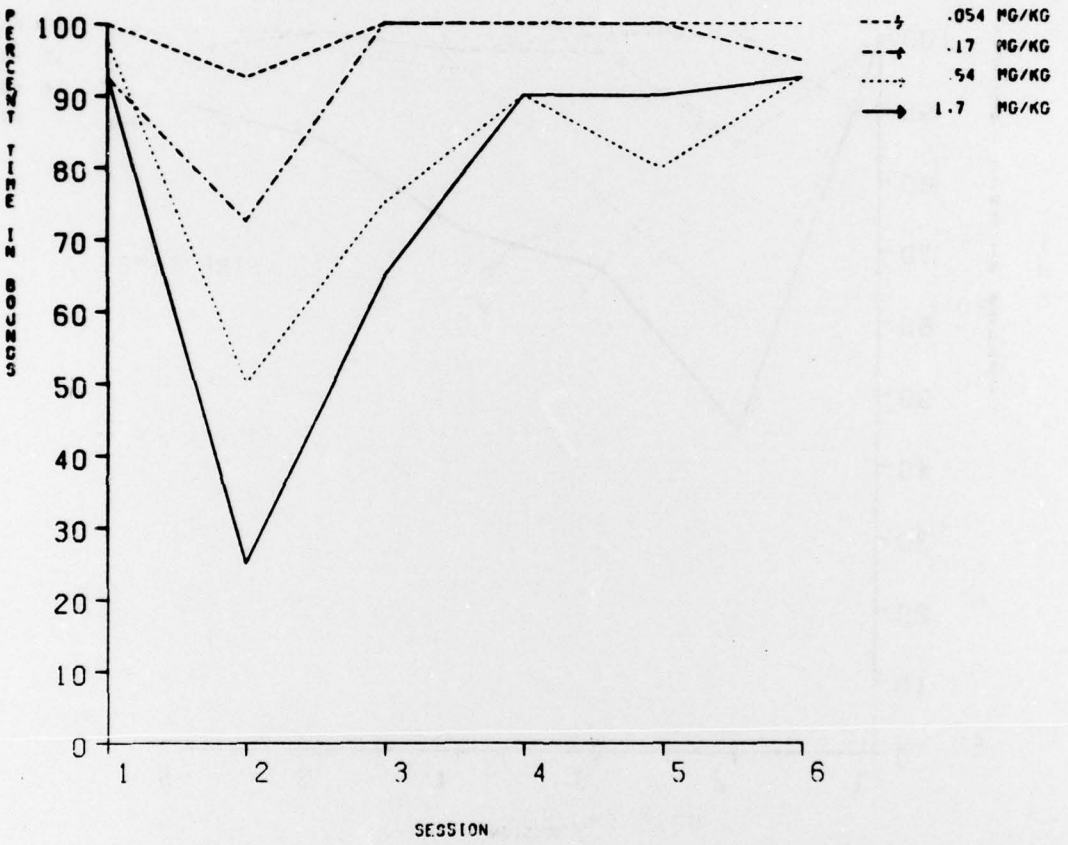

Figure 4. The average time within normal baseline limits for adjusted RMS as a function of session and benactyzine dose.

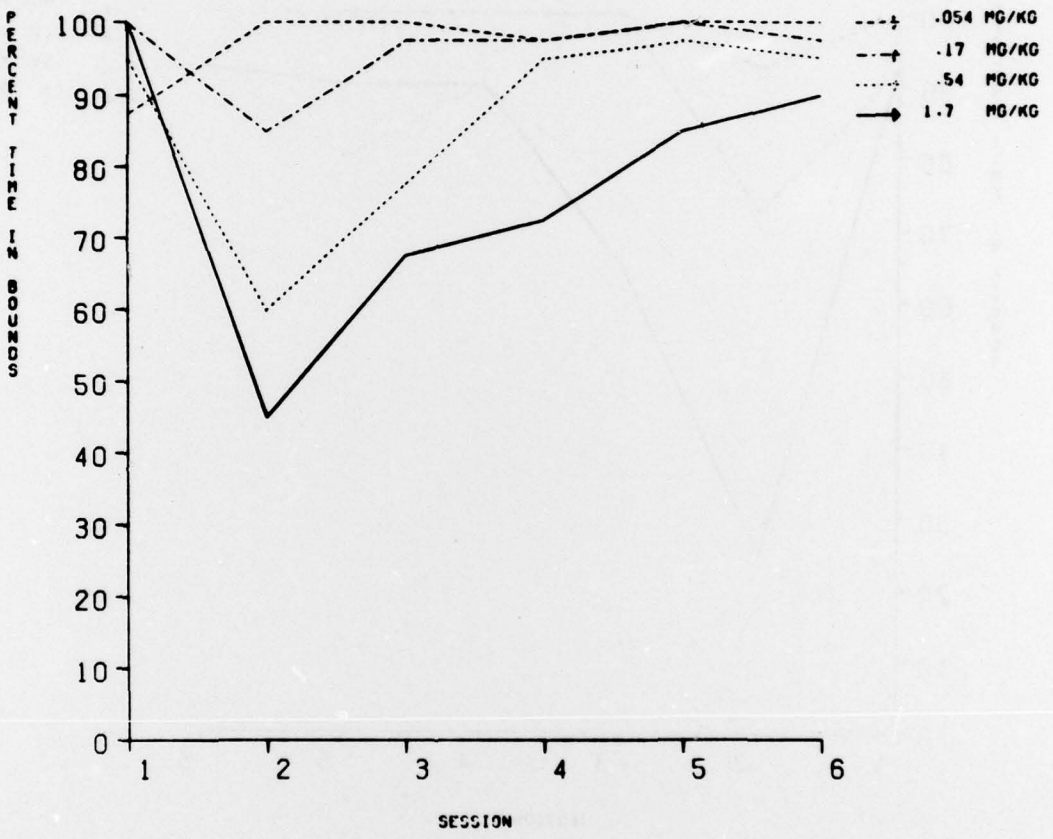

Figure 5. The average time within normal baseline limits for fire time as a function of session and benactyzine dose.

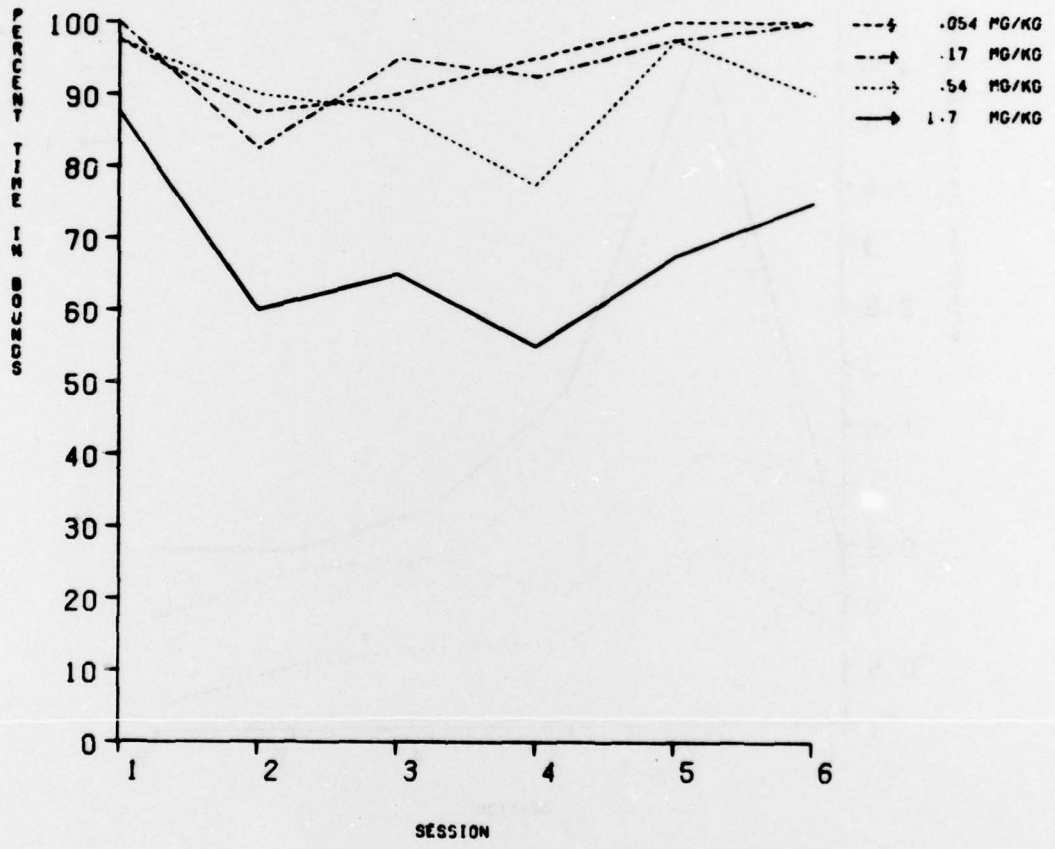

Figure 6. The average time within normal baseline limits for alert time as a function of session and benactyzine dose.

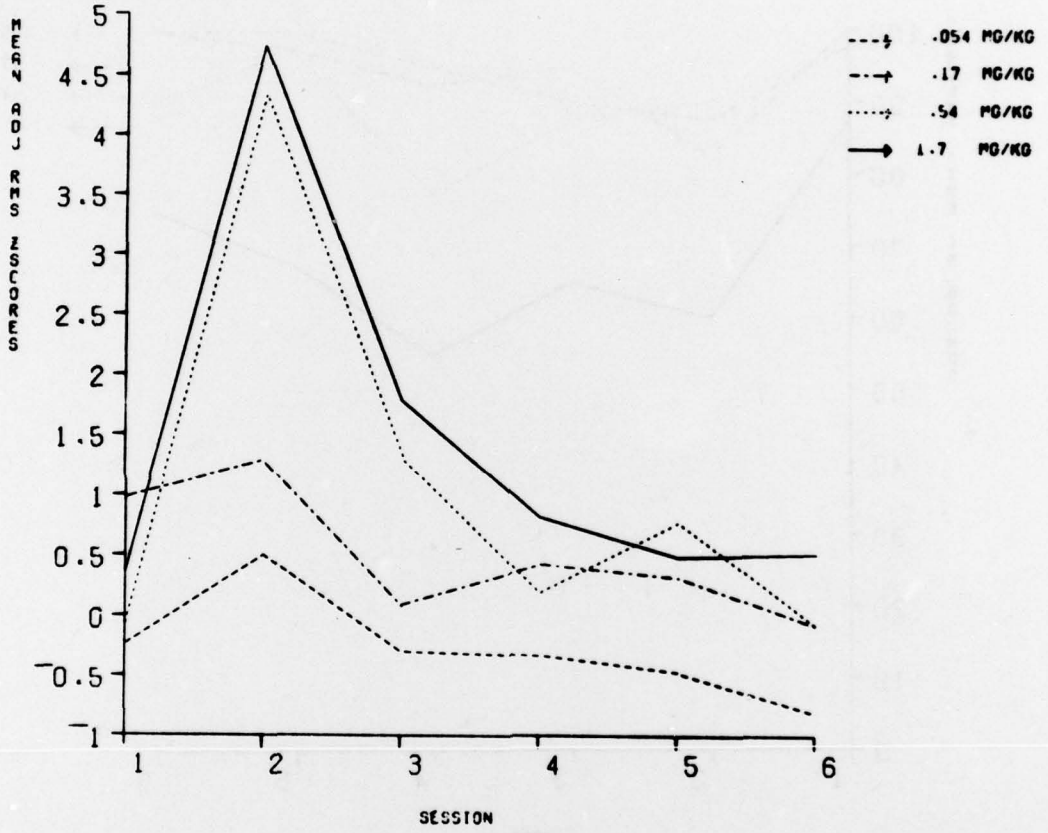

Figure 7. Mean adjusted RMS Z-scores (N=4) as a function of benactyzine dose and time (session).

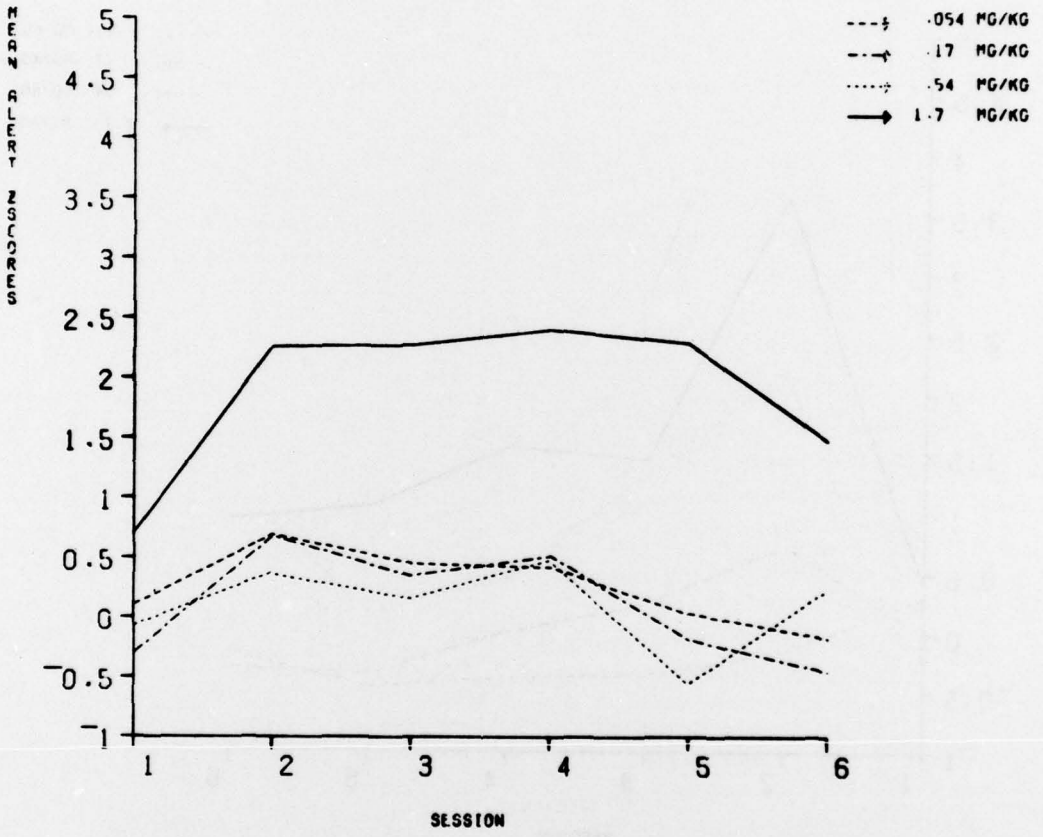

Figure 8. Mean alert time Z-scores (N=4) as a function of benactyzine dose and time (session).

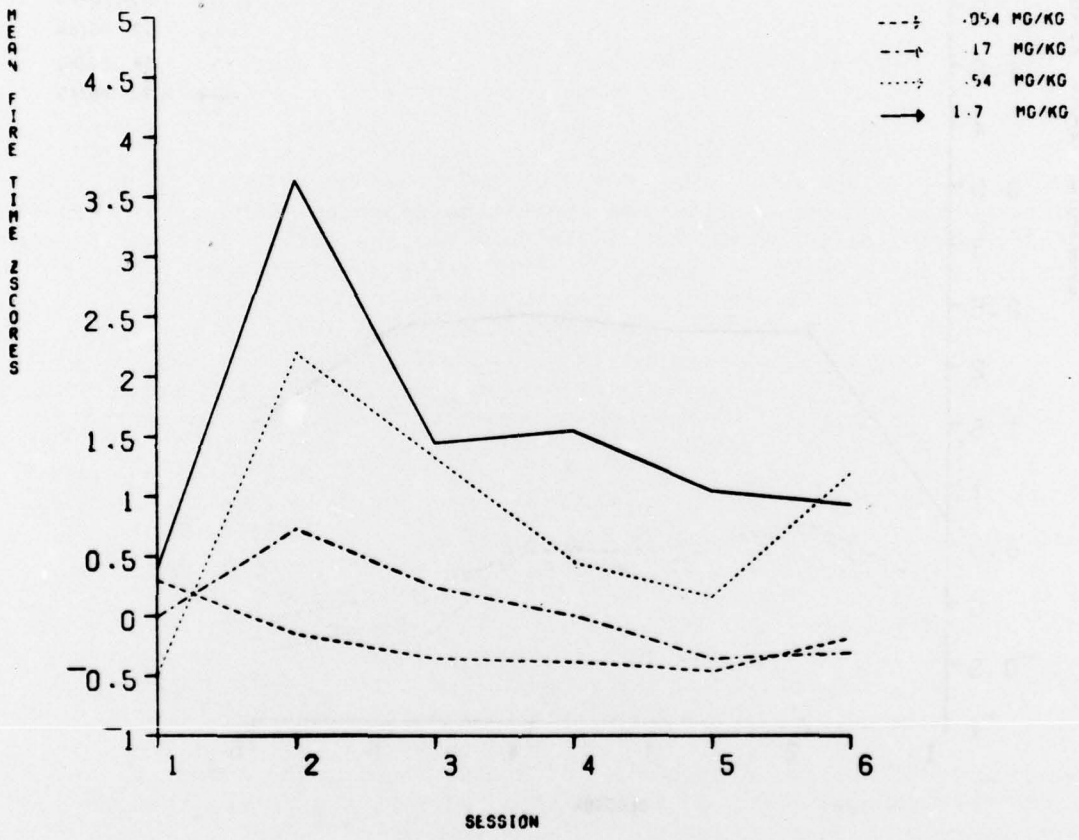

Figure 9. Mean fire time Z-scores (N=4) as a function of benactyzine dose and time (session).

Duncan's multiple range test was used to compare doses by session in the absence of interaction. Testing was conducted at the $\alpha = 0.05$ level and is summarized in Table 4. During session 2, the 1.7 mg/kg dose had significantly greater performance effects than the 0.054 mg/kg dose for both adjusted RMS and mean fire time. During session 5, mean alert times for the 1.7 mg/kg dose were significantly longer than the 0.54 mg/kg alert times. The greatest percentage changes occurred in the adjusted RMS--suggesting that the PEP task was more sensitive than the discrete task.

Worst case or maximum session Z-scores are illustrated in Figures 10-12. Adjusted RMS (Fig. 10) dose-ordering effects are evident and greatest during session 2, with the 1.7 and 0.54 mg/kg doses in excess of 8 standard units. By session 4, the maximum adjusted RMS Z-scores were below 3, suggesting that adjusted RMS could be affected up to 1 1/2 hours postinjection. Worst case alert time Z-scores (Fig. 11) in excess of 3 occurred only for the 1.7 mg/kg dose for the entire test period and for 0.054 mg/kg during session 1.[4] Dose-ordering effects were not apparent for these scores, but clearly reemerged for the maximum fire times (Fig. 12). Fire time scores in excess of 3 lasted the entire 2 1/2 hour postinjection period at 1.7 mg/kg; for the first hour post-injection for the 0.54 mg/kg dose; and only during the first 1/2 hour postinjection for 0.17 mg/kg. There were no Z-scores in excess of 3 for the 0.054 mg/kg dose.

Table 5 summarizes the results of testing. In the absence of interaction, Duncan's multiple range test ($\alpha = 0.05$) found the 1.7 mg/kg dose to be the most debilitating. Maximum adjusted RMS Z-scores and fire time Z-scores were significantly greater than both the 0.054 and 0.17 mg/kg doses during session 2 and for alert times during session 3. Alert times associated with the 1.7 mg/kg dose were also significantly greater than the 0.054 mg/kg dose in session 4 and the 0.54 mg/kg dose during session 5. The 0.54 mg/kg dose was significant during session 2, with RMS scores in excess of the 0.054 mg/kg dose; and the 1.7 mg/kg dose exceeded session 3's 0.54 alert times. Again, the greatest percentage changes occurred in the adjusted RMS, suggesting that the PEP task was more sensitive than the discrete task.

Best case or minimum Z-scores showed the 1.7 mg/kg dose generally dominated the others; however, ordering effects and Z-scores in excess of 3 were not evident so multiple comparison testing was not pursued.

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[4] A single worst case score in excess of 3 during the first session (preinjection) may indicate that the subject was temporarily distracted by initial set-up procedures.

TABLE 4. SUMMARY OF MEAN Z-SCORE EFFECTS

	Session					
	1[a]	2	3	4	5	6
Mean adjusted RMS	NS[b]	1.7>0.054	I[c]	NS	NS	NS
Mean alert time	NS	NS	NS	NS	1.7>0.54	NS
Mean fire time	NS	1.7>0.054	NS	NS	NS	NS

[a]In session 1, trial 2 produced significantly greater mean adjusted RMS scores than trials 3 and 4. Mean alert times were greater for trial 2 than trial 3 in session 6, fire time was greater for subject 4 than subject 3 during session 2.

[b]NS = Nonsignificant with $\alpha = 0.05$.

[c]I = Interaction detected at the 0.05 level by Tukey's test for additivity (cf. ref. 10).

TABLE 5. SUMMARY OF MAXIMUM Z-SCORE EFFECTS

	Session					
	1	2	3	4	5	6
Maximum adjusted RMS	NS[a]	1.7 > 0.17 1.7 > 0.054 0.54>0.054	I[b]	NS	NS	NS
Maximum alert time	NS	NS	1.7>0.17 1.7>0.54 1.7>0.054	1.7>0.054	1.7>0.54	I
Maximum fire time	NS	1.7>0.17 1.7>0.054	I	NS	NS	NS

[a]NS = Nonsignificant with $\alpha = 0.05$.

[b]I = Interaction detected at the 0.05 level by Tukey's test for additivity (cf. ref. 10).

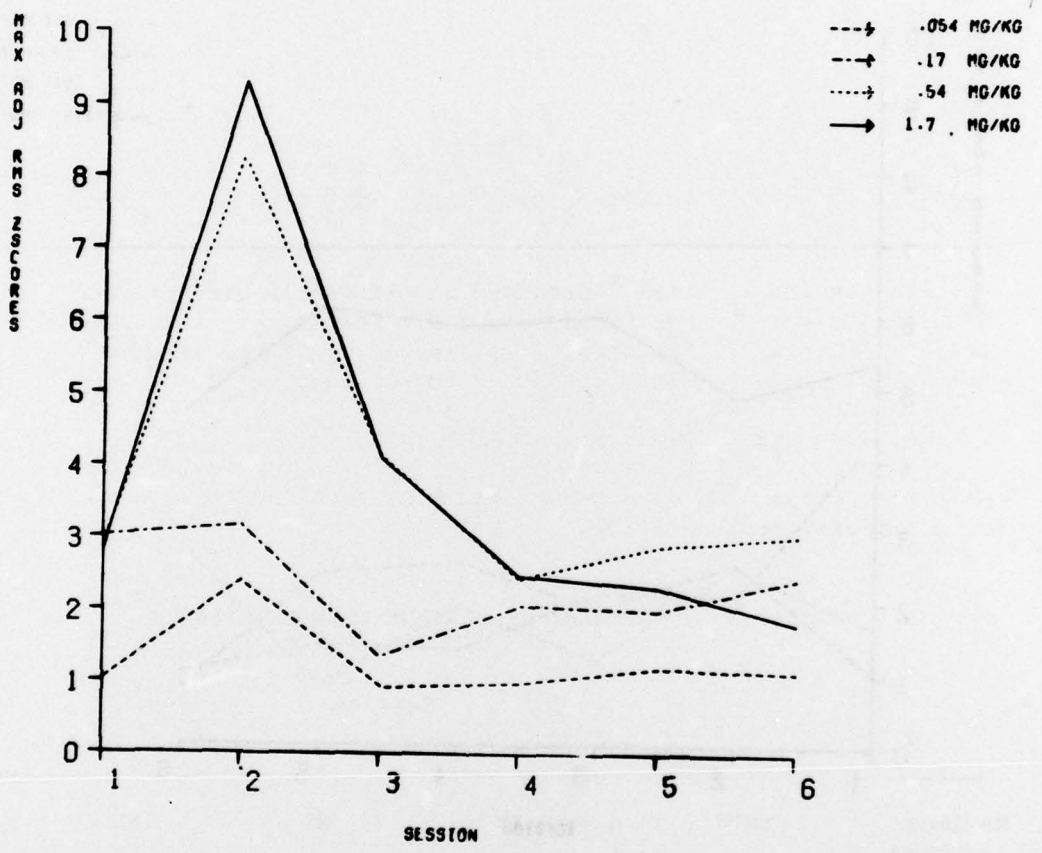

Figure 10. Maximum adjusted RMS Z-scores (N=4) as a function of benactyzine dose and time (session).

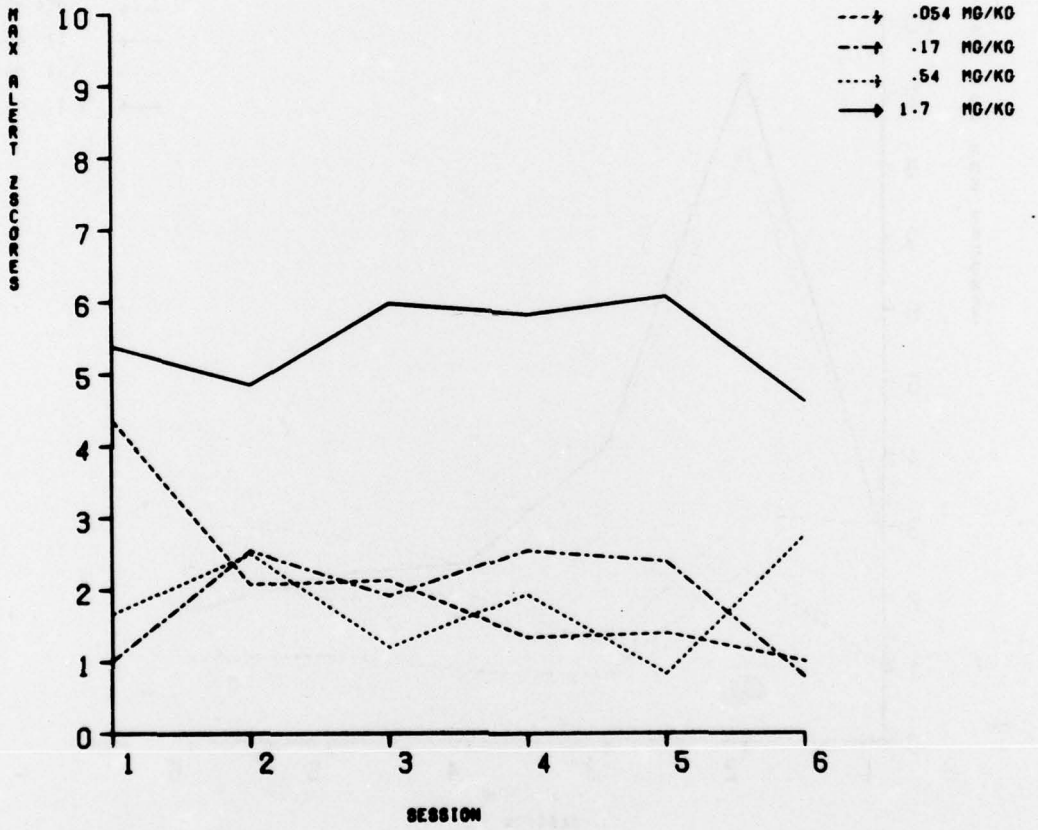

Figure 11. Maximum alert time Z-scores (N=4) as a function of benactyzine dose and time (session).

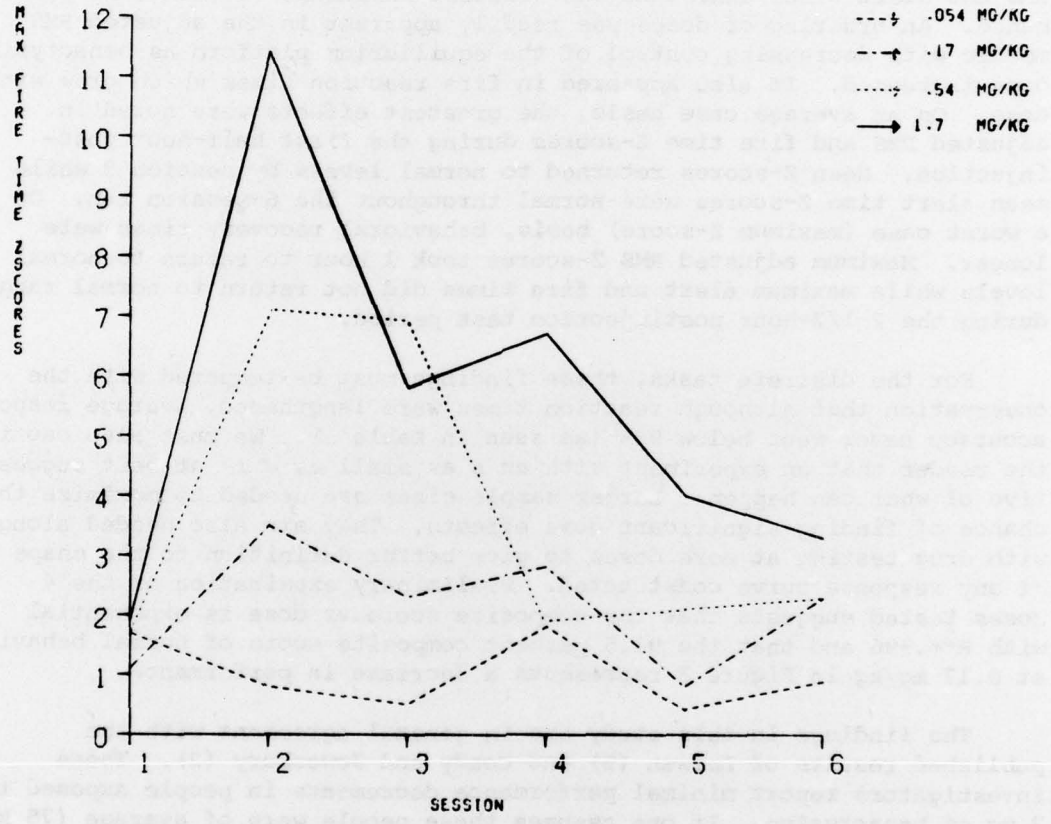

Figure 12. Maximum fire time Z-scores (N=4) as a function of benactyzine dose and time (session).

DISCUSSION

The behavioral responses of 4 Macaca mulatta to 4 different doses of benactyzine (0.054, 0.17, 0.54, and 1.7 mg/kg) have been described. The average time within normal (α=0.05, P=0.95) simultaneous tolerance limits was inversely proportional to the administered doses. Adjusted RMS and alert times exhibited the greatest incidence of change in performance. An ordering of doses was readily apparent in the adjusted RMS metric with decreasing control of the equilibrium platform as benactyzine dose increased. It also appeared in fire reaction times which grew with dose. On an average case basis, the greatest effects were noted in adjusted RMS and fire time Z-scores during the first half-hour postinjection. Mean Z-scores returned to normal levels by session 3 while mean alert time Z-scores were normal throughout the 6-session run. On a worst case (maximum Z-score) basis, behavioral recovery times were longer. Maximum adjusted RMS Z-scores took 1 hour to return to normal levels while maximum alert and fire times did not return to normal ranges during the 2 1/2-hour postinjection test period.

For the discrete tasks, these findings must be tempered with the observation that although reaction times were lengthened, average response accuracy never went below 93% (as seen in Table 3). We must also caution the reader that an experiment with an n as small as 4 is at best suggestive of what can happen. Larger sample sizes are needed to maximize the chance of finding significant dose effects. They are also needed along with drug testing at more doses to give better definition to the shape of any response curve constructed. Preliminary examination of the 4 doses tested suggests that the composite score vs dose is exponential with R^2=.996 and that the 91.5 percent composite score of normal behavior at 0.17 mg/kg in Figure 3 represents a decrease in performance.

The findings in this study are in general agreement with the published results of Larsen (5) and Coady and Jewesbury (2). These investigators report minimal performance decrements in people exposed to 2 mg of benactyzine. If one assumes these people were of average (75 kg) weight, then this dose represents 0.0267 mg/kg. The Yugoslavian study (10 mg benactyzine plus 1 mg pralidoxime) represents a benactyzine dose of 0.133 mg/kg if we make the same 75 kg human weight assumption. Their conclusions of poor ability to aim a rifle and poor ability to run an obstacle course are consistent with the primate data at the .17 mg/kg dose. It is possible that the Macaca mulatta is less sensitive to anticholinergics such as benactyzine, and it is possible that other more sensitive measures may illuminate subtle effects in nonhuman behavior at doses lower than those reported in this study.

It was concluded that 1.7 mg/kg is a debilitating dose of benactyzine in this species, and the maximum sign-free dose is near the minimum of 0.054 mg/kg dose examined in this report. These conclusions are presented based on this 4-monkey experiment and it is acknowledged that larger sample sizes are required to identify either a precise maximum sign-free dose, or a precise dose-response curve for benactyzine.

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